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THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

FEB 5 1975

Application for Research Grant

(Use extra pages as needed)

Date:

1. Principal Investigator (give title and degrees):
Stephen M. Ayres, M.D.
Chairman, Department of Internal Medicine

2. Institution & address:
Saint Louis University
1325 South Grand Boulevard
Saint Louis, Missouri 63104

3. Department(s) where research will be done or collaboration provided:
Medicine

4. Short title of study:
Relationship of Genetic Predisposition, Exposure to High Level Automotive Pollution and Cigarette Smoking to the Development of Chronic Airways Obstruction.

5. Proposed starting date:

6. Estimated time to complete:

7. Brief description of specific research aims:
We plan to evaluate the relationship of three specific risk factors to the development of chronic airways obstruction. The prevalence of predisposing factors and cigarette smoking will be determined in 200 men who have been exposed to high concentrations of automotive pollution for a number of years. Small airway disease will be identified by symptom inventory, measurement of closing volume, and measurement of expiratory flow-volume curves breathing room air and helium. Emphysema will be identified by symptomatology, evaluation of chest radiography, measurement of total lung capacity, and determination of single breath diffusing capacity for carbon monoxide.

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8. Brief statement of working hypothesis: (continued on attached page)

This study seeks answers to the following questions:

Are any or all of the three risk factors related statistically to the development of small airways disease or emphysema?

Are the factors additive or synergistic? Can a table be constructed showing the prevalence of either small airways disease or emphysema with no, one, two, or three risk factors present?

What is the time frame for the development of either small airways disease or emphysema in relationship to onset of initial exposure?

Does small airways disease always progress to emphysema? Does emphysema always follow a period of small airways disease?

Are there specific heterozygous phenotypes determining alpha one antitrypsin concentrations which are related to the development of chronic airways obstruction?

9. Details of experimental design and procedures (append extra pages as necessary)

We have performed yearly studies on over 450 bridge and tunnel officers over the past three years under contract from the Triborough Bridge and Tunnel Authority. This population group is composed of men who collect tolls and control traffic for seven bridges and two tunnels in New York City. These men are exposed to extremely high concentrations of automotive emissions and have high blood carboxyhemoglobin levels. Our study was begun at the request of both Management and Union in order to determine the prevalence of cardiac and pulmonary disease in the population at risk.

An appended reprint details the first two years of experience. Over 75% of the men had laboratory evidence of small airways disease. Figure 1, accompanying this report, shows a Venn diagram depicting the distribution of laboratory and historical abnormalities. Neither detailed smoking or family histories were obtained, but a similar incidence of pulmonary abnormalities were observed in both smokers and non-smokers. In this group, at least environmental pollution rather than cigarette smoking appeared to determine the development of chronic airways obstruction.

The principal investigator will be moving to Saint Louis University School of Medicine as Chairman of Internal Medicine in July 1975. Saint Louis University has traditionally been interested in the determinants of chronic airways obstruction so that the interest of our group in New York City will coincide with established research interests in Saint Louis. Dr. G. O. Broun, Sr. has monitored the importance of viral illnesses to the progression of chronic airways obstruction, and members of the Department of Pathology have contributed to an understanding of the morphology over a period of many years. The availability of expertise in biochemistry, immunology, and the behavioral sciences will improve our ability to achieve the objectives developed in this proposal.

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8. Cont'd.

Is carcinoma of the lung related to genetic and environmental factors as well as to cigarette smoking?

9. Cont'd.

Almost 200 of the 450 bridge and tunnel workers were studied comprehensively during 1972 and 1973. Alveolar carbon monoxide determinations and screening spirometry were performed on-site in the various work locations. They then visited our laboratory facilities on West 12th Street in Manhattan for detailed evaluation. The evaluation included completion of the Cornell Index, completion of a special questionnaire on pulmonary symptomatology based on the British Medical Research Council Questionnaire, physical examination, chest radiography, electrocardiography, clinical laboratory study and pulmonary function study. The pulmonary function evaluation included spirometry, measurement of expiratory flow-volume curves, body plethysmography, measurement of closing volumes and nitrogen washout.

The cohort of 200 individuals form the study group for the proposed research project. We propose to follow their pulmonary function at yearly intervals and attempt to evaluate the prevalence of the risk factors enumerated above.

Pulmonary Function Evaluation: This will be continued on a yearly basis in a manner identical to that performed on the first visit. In addition, flow-volume curves while breathing helium will be obtained because of the recent demonstration that such curves may identify early evidence of small airways disease. Thus far, we have relied on measurements of functional residual capacity and nitrogen washouts to estimate the degree of emphysema. The steady state diffusing capacity for carbon monoxide has been shown to reflect the degree of emphysema and we plan to add this to the yearly evaluation.

Estimation of Exposure to Automotive Pollution: This will be based on the cumulative data of both blood and alveolar carbon monoxide measurements made on-site since the beginning of this study three years ago. Job history, (tunnel or bridge, maintenance, office work) will also be used to evaluate air pollution exposure.

Estimation of Smoking History: A detailed smoking history will be obtained on each individual at the time of initial retesting. This history, together with the Predisposition History described below will be gathered using a personal interview technique. Miss Felicity Reimold has participated in studies of this nature for the past five years and will collect and record the information. The history will include pack-years, type of cigarette smoked, onset of smoking, discontinuation of smoking and years of abstinence if applicable.

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9. Cont'd.

Estimation of Genetic Predisposition: Family history will be evaluated at the time of initial retesting. Specifically, we will ask questions relating to history of pulmonary disease in any family member, history of allergy, tuberculosis, or liver disease.

The prevalence of homozygous or intermediate alpha one anti-trypsin deficiency will be identified by immunodiffusion. This will be performed by Dr. Joseph McKenna at Saint Vincent Hospital and Medical Center in New York City.

Since a key objective of this proposal is to evaluate known biochemical determinants of chronic airways obstruction, subjects with low concentrations of alpha one antitrypsin on immunodiffusion will be studied by starch gel electrophoresis and antigen-antibody crossed electrophoresis to determine phenotype. The laboratory of Dr. John Pierce at Washington University in Saint Louis has had considerable experience with this technique. One of his associates, Dr. Edith Levine will be joining the faculty at Saint Louis University and will assist in the development of this techique.

Supervision of Project: Dr. Darline D. Smith will serve as on-site co-ordinator for the project. She has been responsible for the physical examination and laboratory evaluation for the past year.

Dr. Rodney Coe, Professor of Community Medicine at Saint Louis University and a medical sociologist, will assist in the design and evaluation of the family history and smoking questionnaires. Dr. Lewis Kuller, Chairman of the Department of Epidemiology, University of Pittsburgh, has participated in the design of the entire project.

Data Evaluation: All data is recorded when obtained on data cards designed for the Hewlett-Packard electronic computation system. The storage, retrieval, and evaluation techniques were designed by Mr. Robert Evans who will be responsible for continued processing of data generated by the proposed project.

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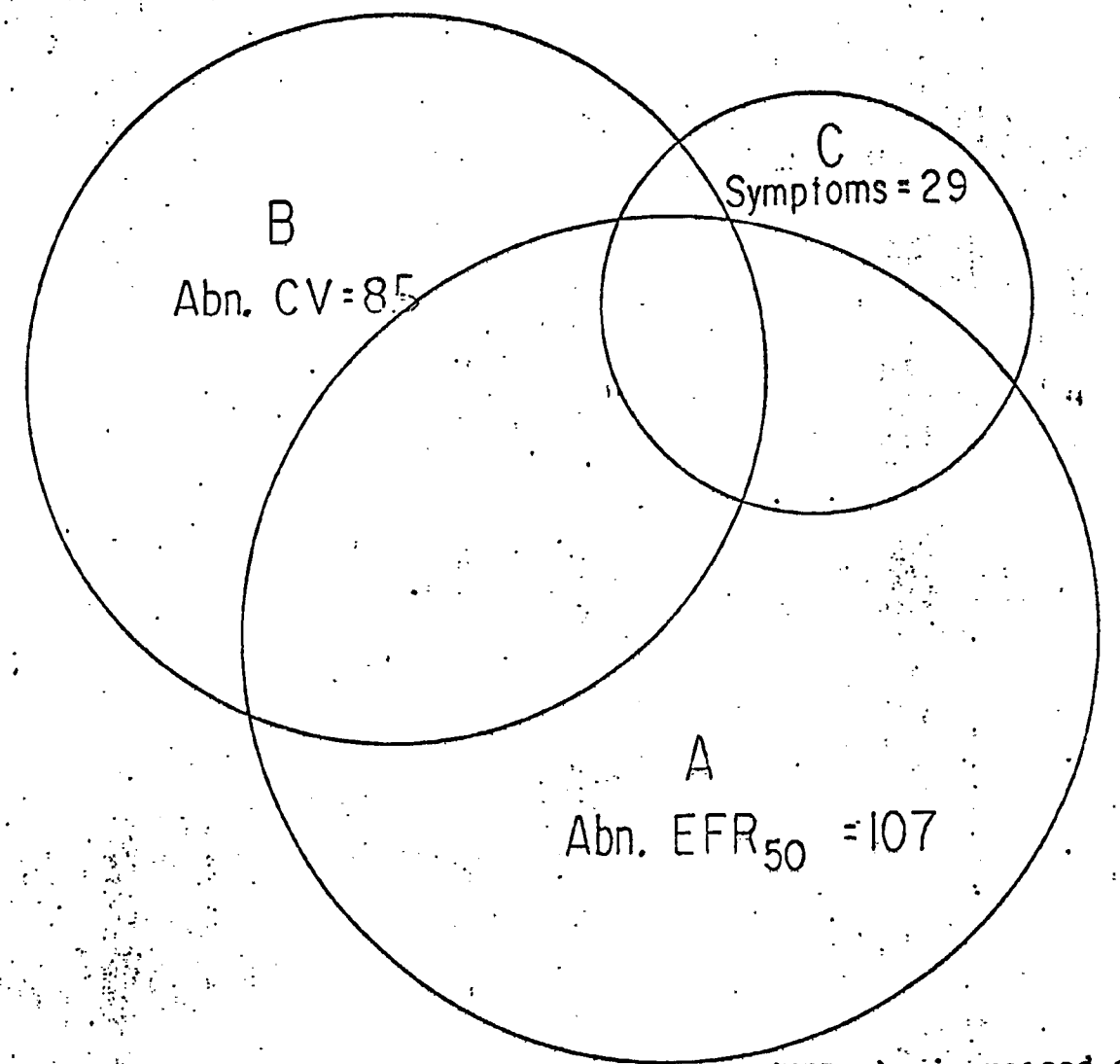

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Figure 1 - Distribution of abnormally low mid-expiratory flow rates (EFR_{50}), increased closing volumes (CV) and symptoms of chronic bronchitis in a population of 111 non-smoking [illegible] and tunnel workers.

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10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Pulmonary Function Laboratory
117 West 12th Street
New York, New York 10011

Dr. J. McKenna
Immunology Laboratory
St. Vincent's Hospital and Medical Center
of New York
153 West 11th Street
New York, New York 10011

Computer facilities
117 West 12th Street
New York, New York 10011

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append):

Please see attached page.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available):

Please see attached page.

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CURRICULUM VITAE

Stephen M. Ayres, M.D.

1929	REDACTED REDACTED
	B.A., Gettysburg College, Gettysburg, Pennsylvania
REDACTED	M.D., Cornell University College of Medicine, New York City
1955	REDACTED
1955-1956	Intern in Medicine, New York Hospital-Cornell Medical Center, New York City
1956-1958	Medical Officer, United States Army
1958-1959	Assistant Resident in Medicine, New York Hospital-Cornell Medical Center, New York City
1959-1960	National Heart Institute Research Fellow, Cardiopulmonary Laboratory, New York Hospital-Cornell Medical Center, New York City
1960-1961	Resident in Cardiology, New York Hospital-Cornell Medical Center, New York City
1961-1963	Director, Cardiopulmonary Laboratory, St. Michael's Hospital, Newark, New Jersey
1961-1963	Clinical Assistant Professor of Medicine, Seton Hall Medical School
1963	Certified, American Board of Internal Medicine
1963-1973	Director, Cardiopulmonary Laboratory, St. Vincent's Hospital and Medical Center of New York, New York City
1964-1968	Assistant Professor of Clinical Medicine, New York University School of Medicine, New York City
1968-1973	Associate Professor of Clinical Medicine, New York University School of Medicine, New York City
1969-1973	Associate Attending in Department of Medicine, New York University Medical Center, New York City
1971	Elected, American Society of Clinical Investigation
1973-75	Physician-in-Chief, Department of Medicine, The St. Vincent Hospital of Worcester, Worcester, Massachusetts
1973-75	Professor of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
1975-	Professor and Chairman, Department of Internal Medicine, Saint Louis University, Saint Louis, Missouri

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Societies:

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Past Appointments:

Member, Medical Advisory Committee, New York City Department of Air Pollution Control
Chairman of Medical Affairs Committee, New Jersey Tuberculosis and Respiratory Disease Association, Inc.
Member, PHS Select Review Committee on Carbon Monoxide, Bureau of Occupation Safety and Health
Board of Directors, Tuberculosis and Respiratory Disease Association of Central New Jersey

Appointments:

Member, Environmental Control Board, New York City (Appointed by Mayor Lindsay)
Member, Mayor's Council on Environment
Board of Directors, National Tuberculosis and Respiratory Disease Association
Chairman, Anti-Smoking Committee
Member, Committee for Guidance of the Respiratory Disease Program
Member, U.S. Surgeon General's Subcommittee on Cardiovascular Aspects of Smoking and Health
Chairman, Committee on Environmental Quality, Medical Society of the State of New York
Member, Medical Advisory Board, American Association for Inhalation Therapy
Chairman, Research Committee of St. Vincent's Hospital and Medical Center of New York, New York City
Board of Directors, Citizens for Clean Air, Inc., New York City
Member, Subcommittee on Environment and Pollution of the Coordinating Council of the Metropolitan Medical Societies
Board of Directors, American Lung Association of Massachusetts

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13. Publications:

1. Ayres, Stephen M., and Buehler, Meta E.: The effects of urban air pollution of health. Clinical Pharmacology and Therapeutics, Vol. 11, No. 3, May-June 1970.

2. Ayres, Stephen M., Giannelli, Stanley, Jr., and Mueller, Hiltrud: Myocardial and systemic responses to carboxyhemoglobin. Annals of The New York Academy of Sciences, Vol. 174, Article 1, October 1970.

3. Ayres, Stephen M., Giannelli, Stanley, Jr., and Mueller, Hiltrud: Carboxyhemoglobin and the access to oxygen. An example of human counterevolution. Archives of Environmental Health, Vol. 26, January 1973.

4. Ayres, Stephen M., Evans, Robert, Licht, David, Griesbach, Jane, Reimold, Felicity, Ferrand, Edward F., and Criscitiello, Antoinette: Health effects of exposure to high concentrations of automotive emissions. Studies in bridge and tunnel workers in New York City. Archives of Environmental Health, Vol. 27, September 1973.

5. Ayres, Stephen M., Giannelli, Stanley, Jr., Mueller, Hiltrud, and Criscitiello, Antoinette: Myocardial and systemic vascular responses to low concentrations of carboxyhemoglobin. Annals of Clinical Laboratory Science, Vol. 3, No. 6, 1973.

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14. First year budget:

A. Salaries (give names or state "to be recruited")	% time	Amount
Professional (give % time of investigator(s) even if no salary requested)		
Dr. Stephen M. Ayres	5%	R
Dr. Darline D. Smith	10%	
Consultations		
Dr. Rodney Coe		R
Dr. Lewis Kuller		
Technical		
Lab Technician	100%	REDACTED
Computer Technician and Data Analyzer	100%	
Sub-Total for A		REDACTED
B. Consumable supplies (by major categories)		
Glassware, gases, chemicals, recording paper and cards	$3,000	
Questionnaire	500	
Sub-Total for B		3,500
C. Other expenses (itemize)		
Reprints and publishing	$ 500	
Computer	1,000	
Travel	1,000	
Sub-Total for C		2,500
Running Total of A + B + C		33,140
D. Permanent equipment (itemize)		
Starch gel and crossed electrophoresis apparatus		3,500
Sub-Total for D		36,640
E. Indirect costs (16% of A-B-C)		4,971
Total request		41,611

15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	REDACTED	$4,000	$3,000	0	$5,528	$42,382
Year 3		4,000	3,000	0	5,976	45,815

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16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Health Surveillance	Triborough Bridge and Tunnel Authority	$70,000	1/71-7/77

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Stephen M. Ayres, M.D.

Signature _____ Date _____

Telephone _____ REDACTED _____
Area Code Number Extension

Checks payable to

Mailing address for checks

Responsible officer of institution

Typed Name _____

Title _____

Signature _____ Date _____

Telephone _____
Area Code Number Extension

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